

What is claimed is:

1. A process for preparing an active pharmaceutical ingredient having a specific surface area of at least about  $5.0 \text{ m}^2/\text{g}$  as measured by B.E.T. comprising:
  - a) storing the active pharmaceutical ingredient at a temperature of below about  $0^\circ\text{C}$ ;
  - 5      and
  - b) micronizing the active pharmaceutical ingredient to obtain a specific surface area of at least about  $5.0 \text{ m}^2/\text{g}$ .
2. The process of claim 1, wherein the storing is carried out at a temperature of about  $-10^\circ\text{C}$  to about  $-20^\circ\text{C}$ .
- 10    3. The process of claim 1, wherein the storing is carried out for at least about 4 hours.
4. The process of claim 3, wherein the storing is carried out for at least about 24 hours.
5. The process of claim 1, further comprising the step of storing the micronized active pharmaceutical ingredient at a temperature of below about  $-10^\circ\text{C}$ .
6. The process of claim 5, wherein the temperature is of about  $-10^\circ\text{C}$  and  $-20^\circ\text{C}$ .
- 15    7. The process of claim 5, wherein the storing is carried out for at least about 4 hours.
8. The process of claim 7, wherein the storing is carried out for at least about 24 hours.
9. The process of claim 5, further comprising re-micronizing.
10. The process of claim 9, wherein the re-micronizing yields an active pharmaceutical ingredient having S.S.A. of about  $6.0 \text{ m}^2/\text{g}$  to about  $7.0 \text{ m}^2/\text{g}$ , as measured by B.E.T.
- 20    11. The process of claim 1, wherein mironizing is carried out with a feed rate of about 4kg/hr to about 30kg/hr.
12. The process of claim 11, wherein the feed rate is about 20kg/hr.
13. The process of claim 1, wherein mironizing is carried out with a feed air pressure of about 2bar to about 10bar.
- 25    14. The process of claim 13, wherein the feed air pressure is of about 8bar to about 8.5bar.
15. The process of claim 1, further comprising re-micronizing.
16. The process of claim 15, wherein the re-micrinizing yields and active pharmaceutical ingredient having a specific surface area of about  $6.0 \text{ m}^2/\text{g}$  to about  $7.0 \text{ m}^2/\text{g}$ , as measured by B.E.T.
- 30    17. The process of claim 1, wherein the active pharmaceutical ingredient has low bioavailability or is formulated for extended release.

18. The process of claim 17, wherein the active pharmaceutical ingredient is selected from the group consisting of nifedipine and leuprolide.
19. The process of claim 18, wherein the active pharmaceutical ingredient is nifedipine.
20. The process of claim 18, wherein the process results in nifedipine with a specific surface area of at least about  $5.5 \text{ m}^2/\text{g}$ .
- 5 21. The process of claim 1, wherein the active pharmaceutical ingredient is administered by inhalation.
22. The process of claim 21, wherein the active pharmaceutical ingredient is salmeterol.
23. A process for preparing nifedipine having a specific surface area of at least about 5.0
- 10  $\text{m}^2/\text{g}$  as measured by B.E.T. comprising:
  - a) storing nifedipine powder for a first time at a temperature below about  $0^\circ\text{C}$  for at least about 4 hours;
  - b) micronizing the nifedipine for a first time to obtain a specific surface area of about  $5.0 \text{ m}^2/\text{g}$  to about  $6.0 \text{ m}^2/\text{g}$ , as measured by B.E.T.;
  - c) storing the nifedipine for a second time at a temperature below about  $-10^\circ\text{C}$ ; and
  - d) micronizing the nifedipine of step c for a second time to obtain an specific surface area of about  $6.0 \text{ m}^2/\text{g}$  to about  $7.0 \text{ m}^2/\text{g}$ , as measured by B.E.T.
- 15 24. The process of claim 23, wherein the storing is carried out at a temperature of about  $-10^\circ\text{C}$  to about  $-20^\circ\text{C}$ .
- 20 25. The process of claim 23, wherein the storing is carried out for at least about 24 hours.
26. The process of claim 23, wherein mironization is carried out with a feed rate of about 4kg/hr to about 30kg/hr.
27. The process of claim 26, wherein the feed rate is about 20kg/hr.
- 25 28. The process of claim 23, wherein mironizing is carried out with a feed air pressure of about 2bar to about 10bar.
29. The process of claim 28, wherein the feed air pressure is of about 8bar to about 8.5bar.
- 30 30. A process for maintaining specific surface area of an active pharmaceutical ingredient having a specific surface area of at least about  $5.0 \text{ m}^2/\text{g}$  as measured by B.E.T. comprising the step of storing the active pharmaceutical ingredient at a temperature of below about  $-10^\circ\text{C}$ , wherein the active pharmaceuticcal ingredient retains a specific

surface area within about  $0.5\text{m}^2/\text{g}$  after at least about six months, as measured by B.E.T.

31. The process of claim 30, wherein the active pharmaceutical ingredient is selected from the group consisting of nifedipine, leuprolide and salmeterol.
- 5 32. The process of claim 30, wherein the storing is carried out at a temperature of between about  $-10^\circ\text{C}$  and about  $-20^\circ\text{C}$ .
33. The process of claim 30, wherein the storing is carried out for at least about 24 hours.
34. The process of claim 30, wherein micronization is carried out with a feed rate of about 4kg/hr to about 30kg/hr.
- 10 35. The process of claim 34, wherein the feed rate is about 20kg/hr.
36. The process of claim 30, wherein micronizing is carried out with a feed air pressure of about 2bar to about 10bar.
37. The process of claim 36, wherein the feed air pressure is of about 8bar to about 8.5bar.
- 15 38. A process for preparing a pharmaceutical oral dosage form comprising:
  - a) storing an active pharmaceutical ingredient having a particle size distribution of about 15 to about 30 microns for a first time at a temperature of below about  $0^\circ\text{C}$  for at least about 4 hours;
  - b) micronizing the stored active pharmaceutical ingredient for a first time to obtain an S.S.A. of at least about  $5.5\text{ m}^2/\text{g}$ , as measured by B.E.T.;
  - c) storing the active pharmaceutical ingredient for a second time at a temperature of below about  $-10^\circ\text{C}$ ;
  - d) micronizing the active pharmaceutical ingredient for a second time to obtain a specific surface area of at least about  $6.5\text{ m}^2/\text{g}$ , as measured by B.E.T.;
  - 20 e) storing the active pharmaceutical ingredient at a temperature of below about  $-10^\circ\text{C}$  for a second time; and
  - f) converting the active pharmaceutical ingredient to a pharmaceutical oral dosage form.
- 25 39. The process of claim 38, wherein the active pharmaceutical ingredient is selected from the group consisting of nifedipine, leuprolide and salmeterol.
40. The process of claim 38, wherein the storing is carried out at a temperature of between about  $-10^\circ\text{C}$  and about  $-20^\circ\text{C}$ .
- 30 41. The process of claim 38, wherein the storing is carried out for at least about 24 hours.

42. The process of claim 38, wherein mironization is carried out with a feed rate of about 4kg/hr to about 30kg/hr.
43. The process of claim 42, wherein the feed rate is about 20kg/hr.
44. The process of claim 38, wherein mironizing is carried out with a feed air pressure of about 2bar to about 10bar.
- 5 45. The process of claim 44, wherein the feed air pressure is of about 8bar to about 8.5bar.
46. A process for preparing an active pharmaceutical ingredient selected from the group consisting of nifedipine, salmeterol and leuprolide, having a specific surface area of at least about  $5.5\text{ m}^2/\text{g}$  as measured by B.E.T. comprising:
- 10 a) storing the active pharmaceutical ingredient at a temperature of below about  $0^\circ\text{C}$  for at least about 4 hours; and
- b) micronizing the stored active pharmaceutical ingredient.
47. The process of claim 46, wherein the active pharmaceutical ingredient is nifedipine.
- 15 48. The process of claim 47, wherein micronization is carried out with a feed rate of about 4kg/hr to about 30kg/hr and a feed air pressure of about 2bar to about 10bar.
49. The process of claim 48, wherein the feed rate is about 20kg/hr and the feed air pressure is of about 8bar to about 8.5bar.
50. The process of claim 48, further comprising storing the micronized nifedipine at a 20 temperature of below about  $-10^\circ\text{C}$ .
51. The process of claim 50, further comprising converting the obtained nifedipine into formulation.
52. A process for preparing an active pharmaceutical ingredient comprising:
- 25 a) storing the active pharmaceutical ingredient at a temperature of below about  $0^\circ\text{C}$  for at least about 24 hours; and
- b) micronizing the active pharmaceutical ingredient, wherein the storing results in a minimum increase of about  $0.5\text{ m}^2/\text{g}^2$  in specific surface area compared to micronizing without storing.
53. The process of claim 52, wherein the temperature is of about  $-10$  to about  $-20^\circ\text{C}$ .
- 30 54. A process for preparing a pharmaceutical oral dosage form comprising:
- a) storing an active pharmaceutical ingredient for a first time at a temperature of below about negative  $10^\circ\text{C}$  for at least about 24 hours;

- 5 b) micronizing the stored active pharmaceutical ingredient at a feed rate of about 20kg/hr and a feed air pressure of about 8bar to about 8.5bar for a first time to obtain an S.S.A. of at least about 5.5 m<sup>2</sup>/g, as measured by B.E.T.;
- c) storing the active pharmaceutical ingredient for a second time at a temperature of below about -10°C;
- d) micronizing the stored active pharmaceutical ingredient for a second time at a feed rate of about 20kg/hr and a feed air pressure of about 8bar to about 8.5bar to obtain an S.S.A. of at least about 6.5 m<sup>2</sup>/g, as measured by B.E.T.;
- 10 e) storing the active pharmaceutical ingredient at a temperature of below about -10°C for a second time; and
- f) converting the active pharmaceutical ingredient to a pharmaceutical oral dosage form.

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